Remarks

Claim 6, 26-29, 35-36, 39-43 and 45-46are here amended, and new claims 57-66 have been added. Claims 14-17, 30-34, and 37-38 have been canceled.

As of this amendment, claims 1-13, 18-29, 35-36 and 39-66 are pending in this application.

No new matter has been added. Applicants believe that the claims herein are in condition for allowance, which is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

Claims 6, 29 and 39 have been amended to correct clerical errors. Support for amended claim 29 can be found in Example 39, on p. 39, and in Table 7, p. 40 of the application. Claims 26-28 and 43 are amended for stylistic reasons. Support can be found in Table 6 on p. 39. Claims 29, 36, 39, 41 and 43 have been amended to correct the dependence of each of these claims to a different earlier claim.

Independent claim 35 as amended is directed to an improved method of administering a polysaccharide, the improvement utilizing a compositions producing decreased edematous response in comparison with utilizing unmodified polysaccharide and otherwise identically administered, wherein the improvement comprises utilizing for administration a derivatized reduced polysaccharide composition, and in derivatizing the polysaccharide, providing an extent of derivatization sufficient to produced decreased edematous response of the derivatized composition. Reference to "edematous response" thus supplants the original claim reference to "toxicity", and the claim now speaks in terms of providing an extent of derivatization sufficient ot produce decreased edematous response.

Independent claim 36 as amended is similarly amended, the improvement comprising utilizing for administration carboxymethylated reduced dextran in lieu of dextran, and in carboxymethylating the dextran, providing an extent of carboxymethylation sufficient to produced decreased edematous response of the derived composition. Here too reference to "edematous response" thus supplants the original claim reference to "toxicity", and the claim now speaks in terms of providing an extent of carboxymethylation sufficient to produce decreased edematous response.

Support for these amendments are replete in the specification, see for example p. 47, Table 12, showing decreased edematous response for various degrees of derivatization in the polysaccharide dextran.

New claims 57-66 have been added. New claims 57-58 replace canceled claims 14-17. These new claims 57-66 are directed to improved methods, which are not found in the prior art.

New independent claims 57 and 59 are directed to improved methods of the type for deriving a composition for pharmacological use from a polysaccharide or from a dextran, respectively, the improvement providing a composition producing decreased edematous response in comparison with a composition otherwise identically derived using unmodified polysaccharide or dextran. In claim 57, the improvement comprises reducing and carboxyalkylating the polysaccharide, and in carboxyalkylating the polysaccharide, providing an extent of carboxyalkylation sufficient to produce a decreased edematous response of the derived composition. In claim 59, the improvement comprises reducing and carboxymethylating the dextran, and in carboxymethylating the dextran, providing an extent of carboxymethylation sufficient to produce a decreased edematous response of the derived composition.

New independent claim 64 is directed to a reduced derivatized polysaccharide iron oxide complex which is stable at a temperature of about 121°C, wherein the sodium salt of the complex does not contain an infrared absorption peak in the region of about 1650 cm^{-1} to about 1800 cm^{-1}. Support for this claim can be found in claims 10 and 20 as originally filed, and throughout the specification. See also the description, Fig. 1-2, p. 8, lines 6-10, and p. 22, lines 22-26.

Support for additional limitations can be found in the description as originally filed, see p. 48, lines 10-26; and pp. 20-29, Examples 1-18 describing preparation of various autoclavable derivatized polysaccharides. See further p.48, Example 53, showing for the first time that the extent of carboxymethylation of dextran can decrease edema following administration to a test animal.

The prior art

All claims stand rejected as either anticipated by Maruno et al. (U.S. Patent No. 5,204,457; henceforth referenced as " '457") and by Maruno et al. (U.S. Patent No. 6,165,378; henceforth referenced as " '378"), or as made obvious by Maruno et al. '457, and further in view of Josephson et al. (U.S. patent number 5,160,726), or Lewis et al. (U.S. patent number 5,055,288), or Groman et al. (4,827,945) in further view of Golman et al. (5,985,245).

Claims directed to autoclavability are neither disclosed nor suggested by the prior art

In methods claims 1-13 and 53-56, and compositions claims 18-29, and 64-66, the compositions are autoclavable.

In particular, independent claim 1 is directed to a method of providing an iron oxide complex for administration, the method comprising: (i) producing a reduced polysaccharide iron oxide

complex; and (ii) sterilizing the complex by autoclaving. Claim 53 is similar, but teaches a method of providing a contrast agent for in vivo MRI of a subject, comprising formulating a composition which is a carboxymethylated reduced coated ultrasmall superparamagnetic iron oxide colloid, and terminally sterilizing the composition by autoclaving. None of the prior art show, teach or suggest autoclavability.

Maruno et al. '457 shows a complex of a reduced carboxyalkyl ether of a polysaccharide with a magnetic metal oxide, and a process for preparing this complex. The Maruno et al. patents show only heating to 80°C, and teach away from autoclaving (Maruno et al. '457, col 11 lines 21-32). Maruno et al. '378 is also directed to a polysaccharide-magnetic metal oxide complex consisting of a polysaccharide derivative obtained by carboxyalkyl-etherifying and unsubstituted or substituted aminoalkyl-etherifying a polysaccharide and a magnetic metal oxide. Interestingly, in '378, the complex is sterilized by filtration (col 17 lines 11-12) through a 0.45 μm filter. Clearly the filter sterilization was used because Maruno '487 teaches that autoclaving causes breakdown of the composition, and filter sterilizing avoids this temperature range (col 11, lines 30-32). As mentioned below, Josephson et al. shows that there is increased toxicity associated with autoclaving polysaccharide-based MRI agents (see Josephson et al., Table 1, and col 8 lines 23-26), although Josephson does not address reduced polysaccharides. Neither of the cited Maruno references disclose or suggest autoclaving, the gold standard of sterilization. In fact, both Maruno et al. references teach away from autoclaving.

None of the other references show reduced polysaccharides (as required by present claims 1-13, 18-29, 35-36 and 39-52 and 57-66), for example reduced dextran (claims 3, 8, 9, 24-29, 36-52, and 57-66), let alone reduced carboxyalkylated polysaccharides (claims 6, 22, 57-58, and 65) such as reduced carboxymethylated dextran (claims 7, 8-9, 24, 25, 26, 27, 28, 29, 36, 39-52, 59-63, and 66). In fact, as are discussed below, none of these references disclose or suggest reduced polysaccharides, as required by present independent claims 1, 5, 18, 35, 36, 53, 54, 57, 59, and 64, and all claims dependent thereon, i.e., all the pending claims.

Josephson et al. (U.S. patent number 5,160,726) et al. relates generally to magnetic resonance (MR) contrast agents and their preparation, and particularly to sterilization for production of such agents. See Josephson et al., col 1, lines 14-17.). Josephson et al. teaches generally that autoclaving causes undesirable changes in toxicity of polysaccharide-based MRI contrast agents. Moreover, there are no reduced polysaccharides (as in present claims 1-13, 18-29, 35-36 and 39-52 and 57-66) in Josephson et al., and therefore no reduced derivatized (as in present claims present claims 5-6, 22, 57-58, and 65) or carboxyalkylated polysaccharides (as in present claims 6, 22, 57-58, and 65) in

Josephson et al. There are only unmodified dextran (col 6, lines 9-10), and an arabinogalactan prepared from larch wood. Most importantly, there is no autoclavability of the MRI contrast agents. See col 4, lines 19-21. Josephson et al. fails to remedy Maruno's deficiencies in teaching the presently claimed methods that show methods including autoclaving.

Josephson et al. in fact teaches away from autoclavability. Indeed, Josephson et al. teaches that citrate can be added to compositions, but this is not a reduced polysaccharide. Josephson et al. show that there is increased toxicity associated with this procedure (see Josephson et al., Table 1, and col 8 lines 23-26).

Lewis et al. (U.S. patent number 5,055,288) "...relates to a method for enhancing an MR image (MRI) of the vascular compartment of an animal or human subject." See Lewis et al., col 3, lines 46-52. Polysaccharides used by Lewis et al. are only dextrans, not reduced, nor carboxyalkylated, and not both (see Lewis et al., Example 1, see col 8, line 29; Example 3, col 9, line 43). While Lewis et al. shows autoclaving, it is only after citrate is added (see col 8, lines 50-55). However there is no reduced polysaccharide.

Groman et al. (U.S. patent number 4,827,945) discloses synthesis of iron oxide by precipitation following coating of the precipitated particles with a polymer, for example, a dextran, or a non-polysaccharide material. See Groman et al. col 11, lines 33-35. Classes of coatings, and a specific example of each shown in this patent are: a protein such as human serum albumin; a protein/polysaccharide composite such as albumin/dextran; a polysaccharide such as dextran, starch, and glycogen; and a wax such as ficoll and polyethylene glycol. There are no reduced or carboxyalkylated polysaccharides in Groman et al. therefore Groman et al. teaches nothing about such materials.

Golman et al. (U.S. patent number 5,985,245) shows that "...gastrointestinal tract manganese contrast agents suitable for imaging of the liver may be produced by the incorporation of a reducing compound containing an α-hydroxy ketone group (--C(OH)—CO) as an uptake promoter." [Emphases added.] See Golman et al., col 2, lines 20-24. Golman et al. further shows Dy DPTA-beta-alanine-dextran (molecular weight 70,000). Dy is a metal, dysprosium; DPTA is a chelator for the metal. See Golman et al., col 4, lines 58-59. Similar complexes with Ga (a metal, gadolinium) are shown Examples 2 and 3 of this references (columns 9 and 10). However all of these materials are in fact metal chelation complexes. Further, while dextrans are part of this complex, they are neither reduced, nor carboxyalkylated, and certainly not both.

Thus Golman et al. fails to teach or suggest any compositions which are reduced polysaccharides, or are dextrans, let alone that such methods include autoclavable reduced polysaccharides or autoclavable reduced dextrans.

Since none of these references teaches reduced carboxyalkylated compositions that are autoclavable, none remedy the deficiencies of Maruno, therefore none anticipates the subject matter of the present claims, nor teaches or suggests the subject matter.

Additional limitations exist in various dependent claims that provide additional bases for their allowability over the art of record. Claims 10 and 64 require that no peak is found at a particular point in an absorption spectrum of the compositions herein. Maruno et al. on the other hand, teaches that there is such a peak. See Maruno et al. '378, Figs. 1-4, and '457, Fig. 4-5.

Claims 18-20 and 29 require that the methods and compositions are stable after autoclaving, with respect to certain physical and chemical properties (e.g., stability at particular elevated temperatures, or stability of colloidal suspension without aggregation). None of these claimed characteristics are shown in any of the prior art. In particular, Maruno shows that after autoclaving, a deposit of gel or precipitate is observed ('457, col 11, lines 30-32). In Maruno et al. '378, the composition is merely filter sterilized (col 17, lines 39-40).

Claims directed to decreased edematous response are neither disclosed nor suggested by the prior art

Similarly, claims 35-52 and 57-63 are directed to methods or a product made by these methods which demonstrate decreased edematous response in a subject following administration. None of the prior art show, teach or suggest decreased edematous response in a subject following administration. Particularly, carboxyalkylation (as in present claims 57-58), such as carboxymethylation (as in present claim 36, 39-52, and 59-63), is adjusted to a level so as to produce a decreased edematous response.

The Maruno et al. patents show only an LD_{50}, which measures only one pharmacological effect, which is the most acute measure (death), and fails to address any other pharmacological measure of a composition. (Table 8, showing a range of the lethal dose is 28 to 120 mmol(Fe)/kg in five week old mice). Moreover, there is no teaching in Maruno et al. nor in any other cited reference to adjust the amount of carboxyalkylation, let alone carboxymethylation, to as required by these present claims.

Josephson et al. shows that administering autoclaved dextran magnetite with citrate causes a significant drop in blood pressure ("+++" grade of response), even when administered at one-tenth the dose of filter sterilized material that is otherwise identical. Josephson et al. shows nothing about

the presently claimed methods of adjusting the amount of carboxyalkylation or carboxymethylation of a reduced polysaccharide, to produce a decreased edematous response, nor does Josephson et al. teach or suggest such methods.

Lewis et al. (U.S. patent number 5,055,288) also adds citrate to the complex in Example 1, prior to sterilization by autoclaving (col 8, lines 52-55), and presumably the toxicity problems in Josephson et al. are also found in Lewis et al. Further, Lewis et al. shows nothing about the presently claimed methods of adjusting the amount of carboxyalkylation or carboxymethylation of a reduced polysaccharide, to produce a decreased edematous response, nor does Lewis et al. teach or suggest such methods.

Groman et al. (U.S. patent number 4,827,945) also uses a polycarboxylic buffer (Groman et al., col 15, lines 49-50), none of which are even polymers, let alone polysaccharides, let alone reduced polysaccharides; all are low molecular weight organic acids. In showing autoclaving of these buffers, Groman et al. is presumably dealing with the same toxicity issues as Josephson et al. Note that these three patents (Josephson et al., Lewis et al., and Groman et al. share common inventors and assignee.) In fact, no toxicity data of any sort are taught or suggested for any compositions by Groman et al., and this reference shows nothing about the presently claimed methods of adjusting the amount of carboxyalkylation or carboxymethylation of a reduced polysaccharide, to produce a decreased edematous response, nor does Josephson et al. teach or suggest such methods.

Golman et al. (U.S. patent number 5,985,245) shows that "...gastrointestinal tract manganese contrast agents suitable for imaging of the liver may be produced by the incorporation of a reducing compound containing an α-hydroxy ketone group (--C(OH)—CO) as an uptake promoter." [Emphases added.] See Golman et al., col 2, lines 20-24.

Further, this reference states, "[p]articularly preferred as an uptake promoter in the compositions of the invention is ascorbic acid which has been found to increase the uptake of manganese...", (see col 2, lines 44-46), and, "[y]et more particularly preferred compositions in accordance with the invention are those in which the uptake promoter is kojic acid;..." (see col 2, lines 53-55). [Emphases added.]

While ascorbic acid and kojic acid may be reducing agents, neither of these is a polysaccharide or even a polymer, but rather low molecular weight acids having molecular weights of 176 and 142 daltons, respectively (see the Merck Index, e.g., 10th Ed., 1983). Golman et al. shows no toxicity data, let alone decreased edematous response when administered, compared to unmodified starting materials. In particular, Golman et al. shows nothing about the presently claimed

methods of adjusting the amount of carboxyalkylation or carboxymethylation of a reduced polysaccharide, to produce a decreased edematous response, nor does Golman et al. teach or suggest such methods.

None of the references cited speak to decreased edematous response when administered. Therefore none of the cited references anticipates, nor renders any of the claims obvious.

Further, the references in combination do not teach or suggest the elements of the claims. None of the other references remedy the defects of Maruno et al. in teaching or suggesting the elements required of the claims. None of the references alone teaches any of the methods or compositions of any of the present claims, as none provides any, let alone all, of the elements of each claim. None of these references can be used in combination to reconstruct the invention of the present claims, as shown below.

Maruno et al. as noted above teaches away from autoclaving. Josephson et al. confirms teaching away from autoclaving, and further, Josephson et al. adds toxicity data showing that autoclaving has an undesirable effect of increasing toxicity. Therefore this combination of references not only clearly fails to teach or suggest autoclaving as an element of a method or a formulation of a polysaccharide, or autoclaving of a complex of a polysaccharide and a metal, but would specifically teach one of ordinary skill not to autoclave.

Josephson et al. is the third and most recent in a series of patents starting with Groman et al. and Lewis et al. cited here, all three of which are commonly owned and invented (along with the present invention). The earlier two patents, *viz.*, Groman et al. and Lewis et al., are the initial teachings of this group of inventors, and as such are not as convincing as Josephson et al. is on any shared point that would represent the cumulative teachings of this group of inventors.

One of skill in the art would look to the teachings of Josephson et al., as the latest of those three commonly owned patents, to represent the most recent and best conclusions of this series. As Josephson et al. teaches away from autoclaving, and is the most recent of the cited patents issued to this group and company, Josephson et al. for the reasons described *supra* fails to teach or suggest the elements of the present invention, so do the earlier cited patents also fail.

Further, Golman et al. neither teaches nor suggests autoclaving, either of a polysaccharide or of a complex. Further, an attempt to combine the references would not result in the present invention. For example, including a reducing agent in a pharmaceutical formulation, as taught by Golman, would have led, in the context of Maruno et al., to methods and compositions that include sodium borohydride, or molecular hydrogen plus a catalyst, in the formulations, or with Groman et al. in the citrate buffers. Alternatively, the showings of Golman et al. might have led one of ordinary

skill to reducing a dextran or a derivatized dextran with an acid such as kojic acid or citric acid, which is not the subject matter of the present claims, or even necessarily feasible.

Therefore the claims are not obvious in light of any of the prior art of record, alone or in any combination. Applicants respectfully request that rejection of claims under 35 U.S.C. § 103(a) be withdrawn.

Claims particularly point out and distinctly claim the subject matter

Claims 5, 10-12, 14-15, 21-22, 26-30, 33-35, 37, 40, and 53-54 are rejected under 35 U.S.C. §112 second ¶ as being indefinite.

The Office Action on p. 2 alleges that the term "derivatized" in claims 5, 10-12, 21-22, 26-29, and 35 is vague.

Applicants believe that the term is both defined in the description of the present application, and is old and well-known term to one of ordinary skill in the chemical arts. Applicants refer to support in the present description for the precise usage of this word, at p. 5, lines 15-19, which states: "...the reduced polysaccharide is derivatized, for example, the reduced derivatized polysaccharide is a carboxyalkyl polysaccharide. The carboxyalkyl is selected from the group consisting of carboxymethyl, carboxyethyl, and carboxypropyl."

From this description, it is clear that the term "derivatized" is not vague, and is defined both generically in the context of this application as a carboxyalkyl derivative of the polysaccharide of the invention, and is also defined specifically, through teaching the examples of carboxymethyl, carboxyethyl, and carboxypropyl derivatives.

Applicants also cite two classical chemical sources for proper definitions and uses of this word. See Ch. 16, p. 594 of Organic Chemistry by Vollhardt et al., Freeman an Co., 2nd Ed., 1994, entitled, "Electrophilic Attach on Derivatives of Benzene," and Ch. 21, p. 823, entitled, "Amines and Derivatives". See also Ch. 2.9, p. 18 of The Systematic Identification of Organic Compounds, by Shriner et al., John Wiley, 6th Ed., 1980, which is entitled, "The Preparation of Derivatives"; and pp. 134-135 recalling the role of derivatization in identifying and characterizing organic compounds prior to the advent of modern spectrographic technologies. Copies of these pages are appended here for the Examiner's convenience. It is clear from these definitions that a chemical derivative is still the original starting chemical, having addition of a simple substituent. The claims as filed distinctly point out and claim the subject matter intended by the term.

For any of these these reasons, use of the term "derivatized" in claims 5-6, 10-12, 21-22, 26-29, and 35 conforms with requirements of 35 U.S.C.§112 second ¶ 112.

The Office Action on p. 3 alleges that the term "native" in claims 14, 30, and 37 is vague and indefinite, and states that it is not clear what this term conveys to the meaning of dextran as a chemical compound. Claims 14 and 30 have been canceled.

In fact, the description of the present application defines the term "native" as the form obtained from nature and obtained from the supplier, compared to another polysaccharide composition which has been reduced. See at least p. 33, lines 27-28 which state, "[c]olloids were prepared using non-reduced (native) dextrans as described for reduced dextrans..." This reference indicates accordingly that native dextrans are non-reduced dextrans.

See also p. 35, lines 34-37, for example, "Preparation of USPIOs coated with carboxymethyl native dextran T10 and carboxymethyl reduced dextran T10 containing varying degrees of carboxymethylation." This title clearly indicates that the term "native" specifically refers to a dextran which is not reduced.

See also Fig. 4 of the cited reference U.S. patent number 5,055,288, Lewis et al., wherein the term "native" as applied to a dextran is used without further explanation.

See further U.S. patent number 2,746,906, issued May 22, 1956 that uses the term "native" to mean the naturally occurring dextran isolated from a bacterium *Leuconostoc meserentoides* without further chemical modification.

As these references indicate, use of the term "native" in two much earlier issued patents, to mean an original dextran having no further chemical alteration, is evidence that one of ordinary skill in the art of polysaccharide chemistry would know that "native" means naturally occurring polysaccharide, not chemically altered in comparison to it's the material at its source. The term "dextrin" cited by the Office Action would not be considered an "unmodified dextran" since dextrin and dextran are chemically different compounds *ab initio*.

Nevertheless, Applicants have amended claims 37 and 38 to replace this word with another term that is standard in the chemical arts, *viz.*, "unmodified".

The Office Action alleges that the phrase "plasma extender" in claims 15, 33-34, and 40 vague and indefinite. Applicants assert that this is a commonly used term by those of ordinary skill in the pharmacological arts. The term defines a type of therapeutic agent, much as the terms anti-infective, analgesic, and anxiolytic describe different classes of therapeutic agents. Further, all of these terms are self describing.

Information obtained by an internet search using the phrase "plasma extender" and the search engine GoogleTM provided 3,070 items in 0.81 seconds. The first 10 items include reference to "serum albumin", "polyvinyl pyrrolidone" (PVP), "gelatin", and a BioTime Report issued January

22, 1998 referring to "...Hextend, a commodity-based plasma extender product." Further items located in this search concerning plasma extenders and blood plasma extenders include: an item by Medtronic, Inc. that PVP was first used as a blood plasma extender during World War II, and is compatible with natural living tissue; a definition of plasma extender as "a physical material which can be transfused into the blood to maintain fluid volume" in BioSpace; and a note that Abbott Laboratories partnered with BioTime in 1999 to bring the latter's first product to market, which was adopted by thousands of physicians in hundreds of hospitals around the U.S.

The Internet search supports Applicants' contention that the term "plasma extender" is well-known to one of ordinary skill in the art, and that the meaning of this term is clear.

The Office Action states that "enhanced" in claim 45, and "ultrasmall" in claims 53-54, are relative terms which render the claims indefinite, and that the specification does not provide a standard for ascertaining the requisite degree, and that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The term "enhanced" in claim 45 has its ordinary meaning, which is "[t]o increase or make greater, as in value, cost, beauty, or reputation; augment". See American Heritage Dictionary of the English Language, 1979, Boston: Houghton Mifflin.

In the art of imaging agents and other fields that provide pictorial data, the term "enhanced" is frequently found modifying the term "image". As shown in the present application, Figures 6-8 show extraordinarily clear imaging of the vascular system, in three different subject species (rat, pig, and human). The images are clear even to the untrained eye, and further show that a low dose of a presently claimed composition can light up the vascular system, including heart, surrounding arteries, and veins, with great contrast against a dark background. See p. 9 of the present application, for the Detailed Description of the Drawings for Figure 8. Applicants assert that one of ordinary skill in the art of MRI would recognize the images as "enhanced", in comparison to those obtained with many other agents.

The Office Action is mistaken as to the term "ultrasmall", when this word is used in the context of "ultrasmall supermagnetic iron oxide" (USPIO). This term is defined in the present application on at least p. 8, line 8, and Table 5 on p. 35. The present application makes reference to the issued patent by Lewis et al. (U.S. patent number 5,055,288), which describes superparamagnetic iron oxides, see col. 9, lines 29-30). Superparamagnetic iron oxides are also described in Josephson et al., U. S. patent number 5,160,726, see at least col 5, line 40. In the present invention, sizes of prior art particles are described on p. 10, lines 6-10, and Tables 5 and 9. As the term superparamagnetic iron oxide is not new, and as the inventor can be his own lexicographer, use of

USPIO to mean ultrasmall superparamagnetic iron oxides is an acceptable designation of one of the products claimed in the application.

Further, contrary to what is alleged by the Office Action, the metes and bounds (the upper limits of sizes of particles) are fully disclosed in Tables 5 and 9 of the present application. For any of the above reasons, the term "ultrasmall" is not vague, is defined fully in the specification and fully complies with 35 U.S.C. §112 second ¶.

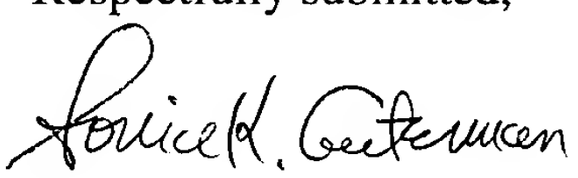
Applicants respectfully request that rejections under 35 U.S.C. §112 second ¶ be withdrawn.

Summary

In view of the foregoing amendments and remarks, Applicant submits that the claims are now in condition for allowance. Early and favorable reconsideration of the application is therefore respectfully requested. The Examiner is invited and encouraged to contact Applicant's representative at the telephone number below if such contact would assist in expediting the present application to allowance.

It is believed that no fee is at present required, however if any fee is required for timely consideration of this application, please charge such fee to Deposit Account No. 19-4972.

Respectfully submitted,



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